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Enantioselective Rh(I)-Catalyzed Cyclization of Arylboron Compounds onto Ketones

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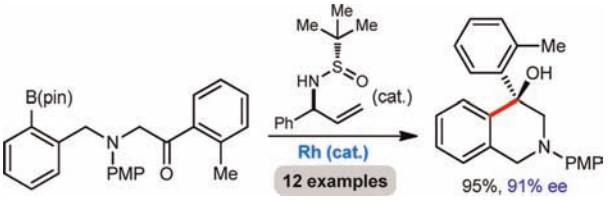
ABSTRACT



Rhodium complexes based upon chiral sulfinamide–alkene, TADDOL-derived phosphoramidite, or diene ligands catalyze cyclizations of arylboron compounds onto ketones, generating a variety of products containing five-, six-, or seven-membered rings with good yields and high enantioselectivities.

Enantioenriched chiral tertiary benzylic alcohols are building blocks of broad utility, and of the various methods available to access these structures,[1] the catalytic asymmetric arylation of ketones[2] stands out as being particularly attractive. Due to their availability, relative insensitivity to air and moisture, high functional group tolerance, and generally low toxicity, arylboron reagents are attractive nucleophiles for these reactions. However, compared with the large body of work describing catalytic enantioselective arylations of aldehydes with arylboron reagents,[3−8] the corresponding reactions with ketones are much less developed.[9]

The reason for this disparity is that ketones are more challenging substrates for enantioselective addition

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reactions than aldehydes; not only are ketones less reactive, they also possess a smaller difference in steric properties between the two carbonyl flanking substituents, which renders effective enantiofacial discrimination more difficult. Although enantioselective rhodium- or copper-catalyzed intermolecular additions of arylboron reagents to highly activated ketones such as isatins,[9a−c] trifluoromethyl ketones,[9d] α-ketoesters,[9e−g] and 1,2-diketones[9g,h] have been reported, effective corresponding methods for ketones lacking strong electron-withdrawing groups have yet to be devised.[10,11]

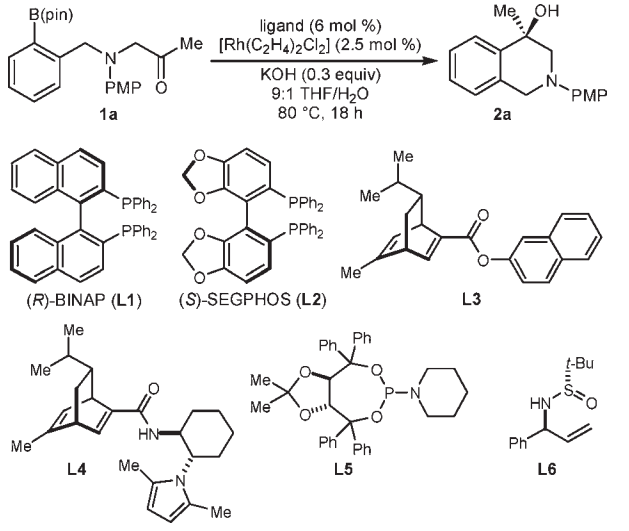
One method to compensate for the lower reactivity of unactivated ketones is to tether the ketone to the arylboron compound, which would result in highly valuable cyclic tertiary-alcohol-containing products.[12] Catalytic enantioselective cyclizations of arylboron compounds onto ketones have been described by Lin and Lu using a Pd−bisphosphine complex[13] and by Kanai, Shibasaki, and co-workers using a chiral Cu−bisphosphine complex.[14] Very recently, the Sarpong group reported the enantioselective synthesis of indanols using rhodium−bisphosphine-catalyzed intramolecular hydroarylations of ketones.[15] It should also be mentioned that Yin, Kanai, and Shibasaki recently reported the intramolecular palladium-catalyzed enantioselective hydroarylation of α-ketoamides using aryl triflates.[16]

Although these methods successfully demonstrate the concept of enantioselective metal-catalyzed intramolecular ketone hydroarylation, challenges remain. First, in all of these examples, only products containing five-membered rings were prepared with high enantioselectivities; cyclizations to form six-membered rings were significantly less selective (46−69% ee).[13a,14,15a,16] Second, in the work of Lu[13a] and Sarpong,[15a] only examples containing relatively unhindered ketones were described; no examples containing sterically hindering substituents such as *ortho*-substituted aromatics or branched alkyl groups were reported. While the work of Kanai and Shibasaki included examples of sterically hindering *ortho*-substituted aryl groups on the ketone, the cyclizations are restricted to the use of highly activated α-ketoamides.[14,16] Therefore, there remains a clear need to address gaps in current methods to enable access to a greater diversity of products, which would further increase the value of metal-catalyzed intramolecular ketone hydroarylation in synthesis.

We therefore recently initiated a program with these considerations in mind, and herein we describe enantioselective rhodium-catalyzed cyclizations of arylboronic esters and acids onto ketones that result in diverse aza-, oxa-, and carbocycles in good yields and high enantioselectivities. The reactions proceed under mild conditions using chiral sulfinamide−alkene, TADDOL-derived phosphoramidite, or diene ligands.

This study began with evaluation of chiral ligands for the enantioselective cyclization of substrate **1a** containing an arylpinacolboronic ester tethered to a methyl ketone via a nitrogen linkage (Table 1). Reactions were performed

Table 1. Evaluation of Chiral Ligands for Cyclization of **1a**



entry	ligand	conversion (%)[a]	ee (%)[b]
1[c]	**L1**	>95	−10
2[c]	**L2**	>95	0
3	**L3**	>95	−8
4	**L4**	>95	−34
5	**L5**	89	−66
6	**L6**	>95	84

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Determined by chiral HPLC analysis. [c] Using 5 mol % of $[Rh(C_2H_4)_2Cl]_2$, 12 mol % of ligand, and 0.6 equiv of KOH. PMP = *para*-methoxyphenyl.

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using $[Rh(C_2H_4)_2Cl]_2$ (2.5 or 5 mol %) as the precatalyst along with the chiral ligand (6 or 12 mol %, respectively) in 9:1 THF/H_2O at 80 °C for 18 h in the presence of KOH. While bisphosphines such as BINAP or SEGPHOS led to efficient cyclizations (>95% conversion), enantioselectivities were low or non-existent (entries 1 and 2). Chiral dienes, which have provided excellent results in various enantioselective rhodium-catalyzed reactions,[17] were investigated next. Unfortunately, α-phellandrene-derived ligands **L3**[18] and **L4**[19] provided the product in low enantioselectivities (entries 3 and 4). Improved results were observed using TADDOL-derived phosphoramidite **L5**,[20] with *ent*-**2a**[2122b] being obtained in 89% conversion and 66% ee (entry 5). Chiral sulfinyl−alkenes have recently emerged as a promising class of ligands for enantioselective rhodium-catalyzed additions of arylboron reagents.[9g,h,22] However, applications to intramolecular reactions have not yet been described, and we were therefore delighted to discover that sulfinamide−alkene **L6**[22b,23] provided the best results among all chiral ligands tested, delivering **2a** in >95% conversion and 84% ee (entry 6).

Figure 1 presents the scope of this process using ligand **L6**. For substrate **1a**, a further increase in enantioselectivity was obtained by performing the cyclization at 50 °C in 30:1 THF/H_2O with a slight increase in rhodium loading (6 mol %) in the presence of K_3PO_4 (0.5 equiv) as the base, which provided **2a** in 82% isolated yield and 89% ee. Under these conditions, a range of other substrates **1b**−**1i**[24] underwent cyclization to give tetrahydroisoquinolin-4-ols **2b**−**2i** in good to excellent yields and generally high enantioselectivities (80−92% ee). In addition to methyl ketones (products **2a**, **2h**, and **2i**) and unhindered aryl ketones (products **2c** and **2f**), the process was tolerant of a sterically demanding *tert*-butyl ketone (product **2b**) and *ortho*-substituted aryl ketones (products **2d**, **2e**, and **2g**). Substrate **1h** containing a *p*-nitrile-substituted arylboronic ester also underwent smooth cyclization, and replacement of the nitrogen substituent from *p*-methoxyphenyl to *p*-chlorophenyl was also tolerated (product **2i**).

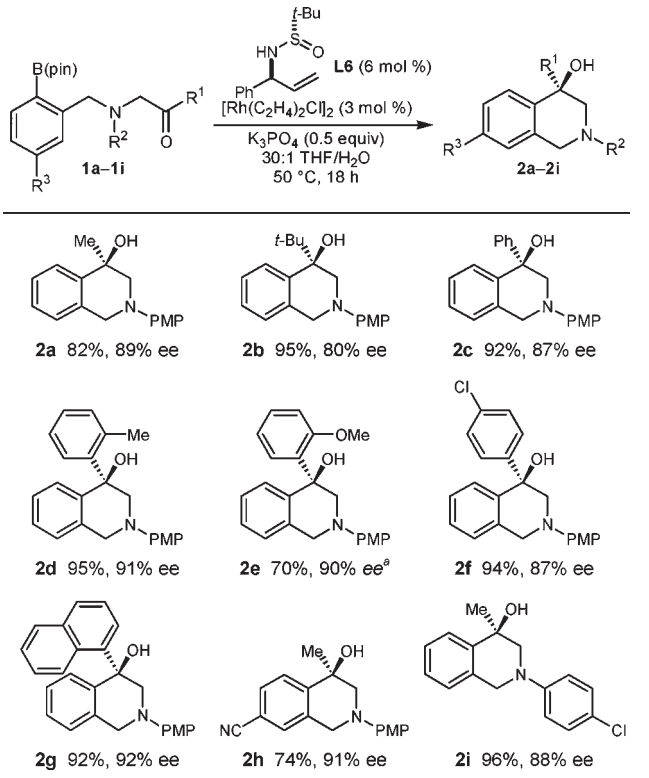
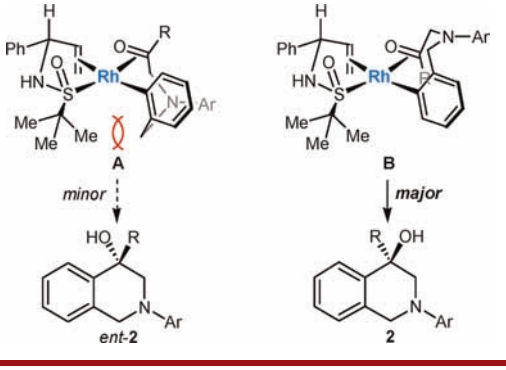


Figure 1. Catalytic enantioselective synthesis of 1,2,3,4-tetrahydroisoquinolin-4-ols. Cited yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. PMP = *para*-methoxyphenyl. [a] Reaction time of 6 h.

Scheme 1 illustrates an empirical stereochemical model that might rationalize the sense of enantioinduction observed in the reactions in Figure 1.[21] First, by comparison with a reported X-ray structure of a chiral sulfinamide−alkene−rhodium complex, it can be predicted that **L6** will bind to rhodium through the sulfur lone pair and the *re* face of the vinyl group. Second, transmetalation of the arylboronic ester in the substrate to rhodium is likely to position the aryl group *trans* to the vinyl group, which has the higher *trans* effect of the two ligand donor sites.[25] Third,

Scheme 1. Possible Stereochemical Model for the Formation of **2**



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(21) The absolute configurations of the products obtained in Tables 1 and Figure 1 were assigned by analogy with that of **2d**, which was determined by X-ray crystallography. See Supporting Information for details.

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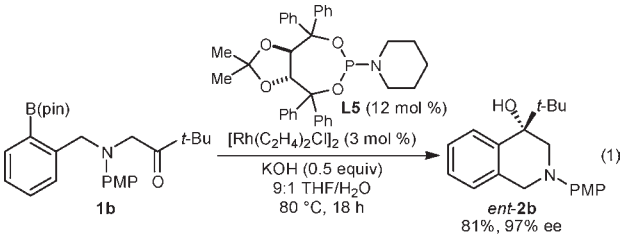
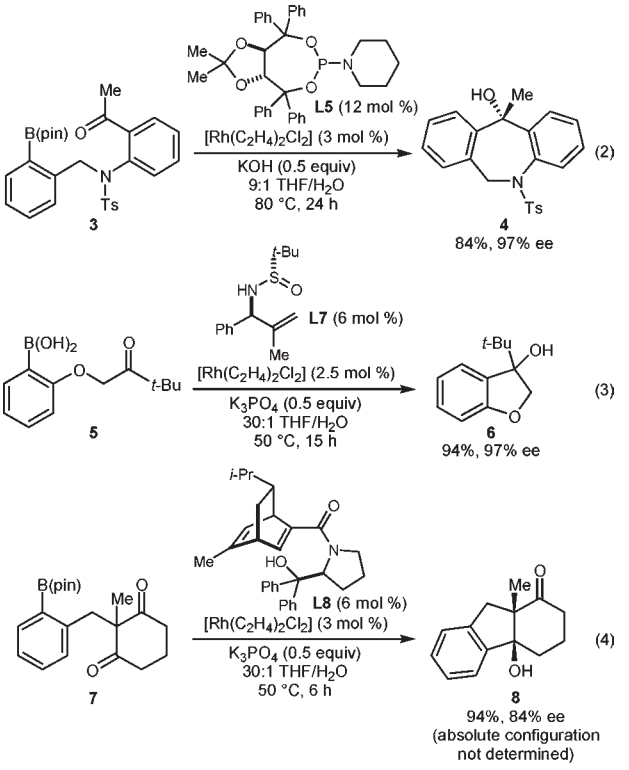
(24) See Supporting Information for the structures of **1b**−**1i**.

arylrhodation of the ketone should proceed via conformations where the aryl−rhodium bond is aligned with the carbonyl group. Two conformations fulfilling these conditions are depicted in Scheme 1. In conformation **A**, the tether connecting the aryl group to the ketone suffers an unfavorable steric interaction with the sulfinyl *tert*-butyl group. However, in conformation **B**, the tether lies on the opposite side of the *tert*-butyl group with respect to the Rh(I) square plane, and reaction through this conformation explains the observed stereochemical outcome.

Although the cyclization of substrate **1b** containing a *tert*-butyl ketone produced **2b** in 80% ee under standard conditions (Figure 1), use of TADDOL-derived phosphoramidite **L5** in place of ligand **L6** under slightly modified conditions (KOH instead of K_3PO_4 and a reaction temperature of 80 °C) led to a marked improvement in enantioselectivity, giving *ent*-**2b** in 97% ee (eq 1). However, the superior enantioselectivity afforded by **L5** compared with **L6** in the cyclization of **1b** was not replicated in the other examples in Figure 1, and **L6** remains the best ligand overall for this substrate class.



The process is not limited to the production of six-membered azacycles; cyclization of substrate **3** using phosphoramidite **L5** provided seven-membered dihydrodibenzo[*b*,*e*]azepin-11-ol **4** in 84% yield and 97% ee (eq 2).[26] Oxacycle synthesis is also possible, as demonstrated by the cyclization of boronic acid **5** containing a highly sterically congested *tert*-butyl ketone. Using **L6**, dihydrobenzofuranol **6** was obtained in a modest 66% ee, but a new isopropenyl-substituted sulfinamide ligand **L7** gave **6** in 94% yield and 97% ee (eq 3).[27] Finally, the process is applicable to the synthesis of carbocycles. Using a new chiral diene **L8**, 1,3-diketone **7** underwent an enantioselective desymmetrization to give tricycle **8** in 94% yield and 84% ee (eq 4).[28]



In conclusion, highly enantioselective rhodium-catalyzed cyclizations of arylboron compounds onto ketones have been developed. The process allows the synthesis of various five-, six-, and seven-membered aza-, oxa-, and carbocycles and illustrates the utility of sulfinamide−alkene, TADDOL-derived phosphoramidites, and dienes as chiral ligands for rhodium-catalyzed intramolecular additions of arylboron compounds.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The absolute configuration of **4** was determined by X-ray crystallography. See Supporting Information for details.

(27) It should be noted that **L7** was inferior to **L6** for substrates **1a**−**1j**. For example, cyclization of **1a** under the standard conditions employed in Figure 1 but using **L7** in place of **L6** gave **2a** in >95% conversion but in 56% ee.

(28) Cyclization of **7** with **L6** gave **8** with >95% conversion but in <50% ee under a range of conditions.

The authors declare no competing financial interest.